In the Claims:

Please renumber pages 62-66 of the original application papers containing the claims and abstract as pages 105-109.

REMARKS

Favorable reconsideration is respectfully requested in view of the foregoing amendments and the following remarks.

With regard to the Sequence Listing, Applicants have submitted a paper copy of the Sequence Listing in paper form as per the Examiner's request. Amendments directing the Sequence Listing's entry into the specification have also been incorporated herein. The paper copies of the Sequence Listing for the present application is identical to the parent application, and the present paper copies are identical to the computer readable copies in the parent application. Further, Applicants respectfully request that the computer readable copies in the parent application be used to prepare a computer readable copy for the present application.

Applicants believe that in light of the above, the application is now in compliance with 37 C.F.R. 1.821-1.825. A copy of the Notice is also attached as requested by the Examiner.

With regard to the rejection of claims 30-49 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 3-15 of USP 5,264,221, Applicants believe that this rejection has been overcome by the filing of a terminal disclaimer enclosed herewith.

Likewise, Applicants believe that the provisional rejection of claims 30-49 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 37, 41-44, 46-49, and 51 of co-pending U. S. Patent Application No. 08/450,363 has also been overcome in view of the same terminal disclaimer.

Thus, Applicants respectfully request that the rejections of claims 30-49 under the judicially

created doctrine of obviousness-type double patenting be withdrawn.

With regard to the rejection of claims 30-49 under 35 USC § 112, first paragraph, this rejection is deemed to be untenable and is thus respectfully traversed.

Applicants again request the Examiner to review the previously submitted Declaration and reference which demonstrates the usefulness of antibody fragment $F(ab')_2$ in "targeting therapy".

Applicants believe that the specification clearly teaches one skilled in the art how to use the claimed antibody fragments, such as Fab'. Further, Applicants also strongly believe that it is well known to one skilled in the art how to use other antibody fragments, such as $F(ab')_2$ in view of the state of the art at the time of the priority date of the present application.

Based on the Examiner's comments from the parent application, the Examiner believes that the use of the term "antibody fragment" encompasses subject matter which includes antibody fragments such as Fv, Fd, or $F(ab')_2$, which is not described in the specification. However, Applicants strongly believe that the specification clearly describes how to use Fab' fragments in the present invention, and how to use $F(ab')_2$ fragments for the purpose of the present invention

It is well established in patent law that the specification does not need to literally describe "in ipsis verbis" the particular claim language in order for the specification to satisfy the written description requirement of 35 USC § 112, first paragraph. See, for example, *In re Lukach* 169 USPQ 795, 796 (CCPA) 1971. Furthermore, it is sufficient that the specification "convey clearly to one skilled in the art, the information that the Applicant has invented the specific subject matter claimed". See, for example, *In re Wertheim* 191 USPQ 90, 96 (CCPA 1976) and *In re Ruschig* 154 USPQ 118, 123 (CCPA 1967).

It is appropriate for the claims to utilize claim language which does not readily appear in the specification as long as one skilled in the art would impliedly or inherently recognize that the Applicant has invented the specific subject matter claimed. In reviewing the teachings of the specification set forth on pages 1, 3, 12, 36, 37 and 41, it is clear that the inventors did contemplate a pharmaceutical composition or a liposome/antibody conjugate comprising an antibody fragment of the monoclonal antibody.

The specification teaches on page 11, line 18 to page 12, line 17 the method for binding an antibody to the surface of a liposome. It discloses as a preferred method a reaction of a thiolated antibody with a maleimide group existing in a liposome (see page 11, lines 21-24). As methods for thiolation, it teaches (1) the use of SPDP, iminothiolane (methyl-4-mercaptobutyrimidate), or mercaptoalkylimidate, which is conventionally used for thiolation of proteins (page 11, lines 21-24), and (2) reduction of the dithiol group intrinsic to an antibody (page 12, lines 6-9).

The second method (2) mentioned above comprises the use of the thiol group possessed by a Fab' antibody fragment which is formed by the reduction of a $F(ab')_2$ fragment as disclosed on

page 12, lines 9-13 and page 36, line 16, page 37, line 5 (Section a. of Example 7) of the specification.

On the other hand, the first method (1) mentioned above, which is addressed to **thiolation of a protein having no thiol group, like F(ab')$_2$** is carried out in a conventional manner as described, for example, by Wright, S. et al., Advanced Drug Delivery Reviews, 3 (1989), pp. 343-352 (see especially on page 351, lines 18-22 and Table II), and by Traut, R.R. et al., Biochemistry, 12 (1973), p 3266-3273, copies of which have already been made of record. Applicants have also demonstrated from the Declaration of T. Tagawa (Appendix III submitted January 26, 1998) that an Experiment conducted using an antibody-bonded PEG-modified liposome which was prepared by binding F(ab')$_2$ to a liposome in accordance with the above-mentioned Traut's method is clearly well within the state of the art at the time of the priority date and clearly show that the present inventors contemplated the present invention using other antibody fragments such as Fab' and F(ab)$_2$.

Applicants wish to remind the Examiner that the antibody fragments of the present invention must contain an antigen binding site for the purpose of the present invention. The current claims recite that the monoclonal antibody fragments must be bound to the surface of a liposome enclosing an anti-cancer agent or toxin and be capable of specifically binding to a surface antigen of a stomach and colon cancer cell membrane. Accordingly, the antibody or fragment thereof used in the claimed invention is defined by specific amino acid sequences.

Applicants also wish to advise the Examiner that the gist of the present invention resides in the finding of a specific monoclonal antibody defined by the amino acid sequences listed in the

Sequence Listing, which can actually bind to the aimed antigen, and not in the finding that antibody fragments can also be used in the same manner as the antibodies themselves for the purpose of the present invention. In other words, it is not necessary under U.S. practice for the present application to teach what is already widely known or recognized by those skilled in the art as of the priority date of the present application. Since it is well known to one skilled in the art that antibody fragments in the field of "targeting therapy" are used in the same manner as the antibody themselves, it clearly shows that the inventors contemplated the use of such fragments, as well as the antibodies themselves in the field of "targeting therapy". In support thereof, Applicants have previously submitted Dr. Hosokawa's Declaration in which the usefulness of antibody fragment $F(ab')_2$ in "targeting therapy" is experimentally shown. Further, a copy of the reference, Biochimica et Biophysica Acta (880 (1986) p72-77) was also previously submitted, which teaches the usefulness of $F(ab')_2$ in "targeting therapy" (see, in particular, Abstract of the article), as well as demonstrates that the use of $F(ab')_2$ in "targeting therapy" was already widely known and recognized by those skilled in the art as of the priority date of the present application. In other words, the previously submitted Declaration and reference clearly demonstrate that the use of antibody fragments in "targeting therapy" as contemplated by the inventors was well known to one skilled in the art at the time of the invention.

Thus, since it is clear that the present inventors contemplated the use of all antibody fragments capable of specifically binding to the surface antigen of stomach and colon cancer cells for "targeting therapy", Applicants respectfully submit that the application is now in condition for allowance. Such action is thus, respectively solicited.

If, however, the Examiner has any suggestions for expediting allowance of the application or believes that direct contact with the Applicants' attorney will advance the prosecution of this case, the Examiner is invited to contact the undersigned at the telephone number below.

Respectfully submitted,

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